This article has been accepted for publication in THORAX following peer review.
The definitive copyedited, typeset version is available online at 10.1136/thoraxjnl

Title: **Asthma, ECMO and Eosinophils**

Authors: Tom McLellan[1], Chinmay Patvardhan[2], Doris Rassl[3], Huw Steven Jenkins[4], Martin Knolle[5,6], Muhunthan Thillai[1,6]

1. Interstitial Lung Disease Service, Royal Papworth Hospital NHS Foundation Trust, Cambridge, England
2. Critical Care Unit, Royal Papworth Hospital NHS Foundation Trust, Cambridge, England
3. Department of Histopathology, Royal Papworth Hospital NHS Foundation Trust, Cambridge, England
4. Respiratory Department, Mid Essex Hospital Services NHS Trust, Chelmsford, England
5. Asthma and Allergy Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, England
6. Department of Medicine, University of Cambridge

Corresponding author:

Dr Tom McLellan
Interstitial Lung Disease Service,
Royal Papworth Hospital
Biomedical Campus, Cambridge, CB2 0AY
tom.mclellan@nhs.net

Keywords:
asthma, critical care, eosinophil biology, histology/cytology, pulmonary eosinophilia

Word count (excluding title page, references, figures and tables): 1597

Funding:
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing Interests

None declared

Tom McLellan (Specialty Respiratory Registrar)

A man in his 30s, with a history of mild childhood asthma only, went to his local hospital with difficulty in breathing. His presentation was preceded by six days of worsening breathlessness, wheeze and cough. He had been using his mother's salbutamol inhaler and received oral amoxicillin in the community. He was hypertensive, tachycardic and had a respiratory rate of 32 breaths per minute. He could not complete sentences, peak flow measurement or lie flat. Chest auscultation revealed diffuse polyphonic wheeze. Arterial blood gas (ABG) whilst receiving fraction of inspired oxygen (FiO2) 40% revealed pH 7.32, PaO2 9.7kPa, PaCO2 6.7kPa. He had a blood eosinophil count of 0.5 $x10^9$/L, serum CRP 30mg/L with normal renal and liver profiles**.** His chest radiograph (figure 1a) revealed clear lung fields with no pneumothorax or consolidation. He was treated with nebulised bronchodilators, intravenous broad-spectrum antibiotics, magnesium, hydrocortisone and aminophylline before transfer to the High Dependency Unit.

Over 48 hours there was an improvement and treatments were gradually weaned but on day three there was a respiratory deterioration associated with a PaCO2 of 7.6kPa requiring intubation. Treatment was augmented with a ketamine infusion and inhaled sevoflurane. Despite optimum ventilation strategies, four hours after intubation there was severe gas trapping requiring manual decompression, low tidal volumes and a rising arterial PaCO2. A referral to the local extracorporeal membrane oxygenation (ECMO) centre was made.

Chinmay Patvardhan (Consultant Intensivist)

On our arrival, the patient was in ventilatory failure with severe gas trapping. Pre-ECMO ABG (FiO2 60%) showed pH 6.98, PaO2 10.7kPa, PaC02 17.8kPa. Veno-venous ECMO was initiated at 4.9 litres per minute (L/min) flow and sweep of 3L/min without incident and he was transferred to the ECMO centre.

During the first few days, treatment continued with intravenous hydrocortisone, broad-spectrum antibiotics and antivirals. Intravenous salbutamol, ketamine and aminophylline were used as bronchodilating agents. A computerised tomography (CT) scan was performed on day 1 of ECMO treatment. This showed no abnormalities in the abdomen, pelvis, head or neck. ECMO cannulae were appropriately placed. There were a few small patchy areas of consolidation and ground glass (Figure 1b). There were no features of chronic lung disease.

Bronchoalveolar lavage (BAL) for extended bacterial, fungal and viral cultures, including PCR microarray were negative as were serum viral and bacterial screens. Broad spectrum antibiotics were continued, oseltamivir was stopped. The patient was haemodynamically stable and vasopressor support was stopped 3 days after ECMO initiation. Intravenous salbutamol was switched to regular nebulised therapy.

Despite bronchodilation and intravenous steroids, the patient remained obstructed requiring an ECMO sweep flow of 7-8L/min to normalise arterial PaCO2. There was a persistent blood eosinophil count of $1.0x10^9$/L. He required repeat bronchoscopies

because of thick secretions. Chest radiographs showed evidence of right lower lobe collapse. On day 3 of ECMO therapy hydrocortisone was stopped and the patient was pulsed for 3 days with methylprednisolone (0.5-1 gram daily). There was no evidence of malabsorption and he was subsequently treated with prednisolone at 0.5mg/kg daily. His BAL samples were reviewed by the pathology team.

Doris Rassl (Consultant Histopathologist)

A total of five BAL samples were received for this patient. The first was performed on day 1 of ECMO cannulation. The differential cell count was eosinophil rich (35%) (figure 1c). BALs performed during and just after treatment with methylprednisolone on days 8 and 10 showed evidence of reduced eosinophil counts (3 and 5% respectively). There were no haemosiderin laden macrophages or other features consistent with haemorrhage on any sample. Immunophenotyping using flow cytometry showed evidence of normal B and T cell lymphocyte populations. Cytology revealed evidence of branching fungal hyphae.

Chinmay Patvardhan

Whilst methylprednisolone supressed the peripheral eosinophil count, the patient's lack of clinical progress caused concern. BAL and serum galactomannan and Beta-D Glucan levels were normal but amphotericin B was still commenced. The eosinophil-rich BAL raised the possibility of eosinophilic granulomatosis with microscopic polyangiitis (EGPA). After discussion with the regional vasculitis service he underwent plasma exchange between days 8 and 11 of EMCO therapy. This made no difference to his clinical condition. A BAL performed on day 12 of ECMO treatment (after plasma exchange) revealed similar features to earlier investigations

with a rising eosinophil count of 58% (figure 1d). By day 13 the patient remained bronchospastic and it was not possible to further reduce ECMO requirements. An opinion was sought from the Interstitial Lung Disease team.

Muhunthan Thillai (Consultant ILD Physician)

The patient was a current smoker with a 5-pack year history who had never vaped, had childhood asthma but not required inhaled therapy since aged 18. There was no history of peripheral neuropathy, sinus, or skin disease. He took no over the counter or prescribed medication and had used non-steroidal treatment and amoxicillin without incident. There was no history of foreign travel. As a teenager he played football to a semi-professional standard and was now the main carer for his mother. Their accommodation was in good condition without obvious fungus or mould exposure.

Investigations revealed normal protein electrophoresis with a mildly raised total serum IgE of 155kU/L. Aspergillus IgG titres were 17mg/L. Serology for helminths and parasites was normal. Urinalysis, autoimmune and vasculitic screens were bland.

A transbronchial or surgical lung biopsy would have been useful but given the significant ECMO requirements and risk of bleeding this was not performed. Acute idiopathic eosinophilic pneumonia presents with an acute illness and is more common in young men who smoke. Peripheral eosinophilia may be present and a BAL eosinophil count of >25% is part of the diagnostic criteria. However, whilst some patients require mechanical ventilation, this is due to type 1 respiratory failure and

gas trapping is not a feature. The presenting chest radiograph did not show consolidation and whilst there were small patches of ground glass and consolidation on CT, these did not account for the severity of illness. The condition usually responds rapidly to steroid therapy. No agent causing a drug reaction could be identified. The results were not consistent with acute hypersensitivity pneumonitis. A negative antineutrophil cytoplasmic antibody does not exclude EGPA but the short history and single organ involvement made this diagnosis unlikely. The patient did not meet criteria for hypereosinophilic syndrome. A specialist asthma opinion was sought.

Martin Knolle (Consultant Asthma Physician)

The history and results of investigations were reviewed and it was felt an acute asthma exacerbation was still the most likely diagnosis. The cause of exacerbation was unclear, but young patients may present acutely having had sub-clinical symptoms for some time. The presence of fungal hyphae on BAL suggested a potential trigger, but on balance was felt more likely to represent airway colonisation during ECMO treatment. Conventional therapy had not improved his condition. Rescue treatment with mepolizumab was considered and after discussion with the patient's next of kin, 100mg was administered subcutaneously on day 14 of ECMO treatment.

Chinmay Patvardhan

There was an improvement in the patient's condition. He was decannulated on day 16 of ECMO therapy and repatriated, (figure 1c).

Huw Jenkins (Consultant Chest Physician)

After repatriation the patient completed a largely uneventful 4-week admission. The peripheral eosinophil count remained normal and repeat BAL had an eosinophil count of 8%. He was discharged on oral prednisolone and a beclomethasone-formoterol inhaler. Pulmonary function testing at three months revealed FEV1 2.87L (73%) FVC 4.07L (86%), TLCO 73% KCO 103%. He has been followed up for 18 months. Oral steroids have been weaned and there have been no other acute exacerbations or medical presentations. Repeat chest radiographs, serum aspergillus and immunoglobulin results have been normal. His blood eosinophil count has not exceeded $0.4x10^9$/L. His fractional exhaled nitric oxide level is normal.

Discussion

A high lung eosinophil count has a range of differential diagnoses. In this case the obstructive pattern of disease, lack of drug exposure, normal ANCA levels and relatively normal lung parenchyma on imaging pointed towards asthma as the most likely primary cause. ECMO improves survival in near-fatal asthma when mechanical ventilation fails, however a positive response is usually seen within days and the mean duration of treatment in survivors is 7 days (1). This patient required a total of 16 days of ECMO therapy and by day 14 was not showing signs of improvement despite maximal conventional therapy.

Mepoluzimab, an anti-interleukin 5 (IL5) monoclonal antibody, is an effective treatment in severe, chronic eosinophilic asthma (2,3) but is not approved by NICE in the United Kingdom for use in acute exacerbations. The decision to use it was made (after discussion with the family) by specialists with experience of acute asthma, anti-

IL5 therapy and ECMO, who completed the appropriate hospital pharmacy application for off-licence use and were in agreement that the potential benefits outweighed the risks in this specific case. The patient may have improved without mepolizumab therapy but the change in clinical condition 48 hours after administration was striking. To our knowledge, this is the first recorded instance of it being used as rescue therapy in a near-fatal exacerbation. Benraluzimab has a more rapid eosinophil depleting action and has been used successfully in an acute exacerbation (4). However, our unit did not have experience with benraluzimab at the time of use. Mepoluzimab may have a slower time of action but does still begin to reduce the peripheral eosinophil count within 24 hours of administration (5). Despite patient improvement, we cannot prove a causal relationship with drug administration and this, as well as the potential synergistic effect between steroids and anti-IL5 therapy in an acute exacerbation, warrant further investigation. Patients who present with near-fatal asthma require careful long-term assessment in the outpatient clinic to monitor spirometry, treatment adherence and identify triggers.

Contributorship Statement

All authors (TM, CP, DR, HJ, MK, MT) contributed to the conception, design, editing and production of the case report.

All authors contributed to the drafting and revision of the manuscript.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Yeo H, Kim D, Jeon D et al, Extracorporeal membrane oxygenation for life-threatening asthma refractory to mechanical ventilation: analysis of the Extracorporeal Life Support Organization registry. *Crit Care*. 2017 Dec 6;21(1):297.

2. Ortega H, Liu MC, Pavord ID et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014 Sep 25;371(13):1198-207

3. Shrimanker R, Pavord ID, Yancey S et al. Exacerbations of severe asthma in patients treated with mepolizumab. *Eur Respir J*. 2018 Dec 13;52(6).

4. Ramakrishnan S, Camp J, Vijayakumar B et al. 'The Use of Benralizumab in the Treatment of Near Fatal Asthma: A New Approach'. *American Journal of Respiratory and Critical Care Medicine.* 2020 Jun 1;201(11):1441-1443.

5. Moran AM, Ramakrishnan S, Borg CA et al. Blood Eosinophil Depletion with Mepolizumab, Benralizumab, and Prednisolone in Eosinophilic Asthma. *American Journal of Respiratory and Critical Care Medicine* 202, no. 9 (1 November 2020): 1314–16.